

Visual outcomes, safety profile and morphometric response of optical coherence tomography biomarkers to ranibizumab biosimilar treatment in neovascular age-related macular degeneration: Real-world evidence

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Purpose: The aim of this study was to evaluate the safety, efficacy, and morphological response of intravitreal ranibizumab biosimilar (Razumab) in neovascular age-related macular degeneration (n-AMD) up to 12 weeks. **Methods:** Retrospective analysis of 20 eyes of n-AMD receiving 4 weekly intravitreal Razumab. Main outcome measures were mean change in best-corrected visual acuity (BCVA), intraretinal-fluid (IRF), subretinal-fluid (SRF), central-subfield thickness (CSFT), maximum central-retinal thickness (CRT), and dimensions of pigment epithelial detachment (PED) from baseline to weeks 4, 8 and 12. **Results:** Improvement in BCVA was seen at all visits, although not significantly (4 weeks: $P = 0.18$; 8 weeks: $P = 0.4$; 12 weeks: $P = 0.06$). At 12 weeks, 90% of eyes either maintained or had an improvement in BCVA, with 40% of them showing an improvement of ≥ 3 -lines and only 5% of them losing ≥ 3 -lines of visual acuity. The median PED height and PED width reduced by $20.5 \mu\text{m}$ ($P = 0.03$) and $557.5 \mu\text{m}$ ($P = 0.14$), respectively, along with a mean reduction of $57.26 \mu\text{m}$ in CSFT ($P < 0.001$) and $44.15 \mu\text{m}$ in CRT ($P = 0.004$), respectively, at 12 weeks. On qualitative analysis, resolution of SRF and IRF was observed in 45% and 25% of eyes at 12 weeks. There were no serious ocular or systemic side effects identified. **Conclusion:** In real-world scenario, Razumab is an efficacious and economical anti-vascular endothelial growth factor (anti-VEGF) agent for optimal management of n-AMD. The therapeutic outcomes demonstrated reasonable stabilization and improvement in visual acuity, favorable anatomical outcomes pertaining to OCT-biomarkers with an acceptable safety profile.

Key words: Age-related macular degeneration, Anti-VEGF, biosimilars, optical coherence tomography, Razumab

Age-related macular degeneration (ARMD) is a leading cause of irreversible visual impairment amongst elderly population.^[1] In an Indian scenario, it is a primary cause of legal blindness affecting 6.8% of the population between 40 and 79 years of age.^[2] With the advent of anti-vascular endothelial growth factor (anti-VEGF) agents more than a decade ago, the management of neovascular AMD (n-AMD) has undergone a paradigm shift.^[3] The recombinant anti-VEGF drugs bevacizumab (Avastin®; Genentech, S. San Francisco, CA/Roche, Basel, Switzerland), ranibizumab (Lucentis®; Genentech, S. San Francisco, CA/Roche, Basel, Switzerland), aflibercept (Eylea®, Regeneron, Tarrytown, NY), and brolucizumab (Beovu®; Novartis, Basel, Switzerland) are used widely throughout the world for management of various chorioretinal disorders.^[4-6] Ranibizumab, aflibercept, and brolucizumab are approved by the US Food and Drug Administration (FDA) for the management of retinal conditions,^[4-6] while bevacizumab, which is approved for the treatment of several advanced solid malignancies, is used off-label by ophthalmologists.^[7]

In 2015, Razumab® (Intas Pharmaceuticals, Ahmedabad, India) became the first and only biosimilar of Lucentis to be approved by the Drug Controller General of India (DGCI)

for ophthalmic use based on promising results of a phase 3 trial demonstrating its efficacy in 103 eyes with nAMD.^[8] The Razumab clinical trials (RE-ENACT study and RE-ENACT 2 study) have provided encouraging data regarding its safety and efficacy for the treatment of nAMD and retinal vein occlusions (RVO).^[8-12] Majority of the evidence for Razumab usage in clinical practice is based on outcomes of these controlled trials. Although they form an excellent platform for formulating management protocols for management of vitreoretinal disorders, their widespread application is limited as they may not accurately reveal the delivery settings and the population diversities in real-world scenarios. Additionally, there is dearth of literature that analyses the response of intravitreal Razumab on various optical coherence tomography (OCT) biomarkers in n-AMD. Of these, a retinal pigment epithelial detachment (PED) remains a foremost entity, seen in as high as 63-80% of AMD cases.^[12] Without treatment,

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around 40-50% of these PED's may lead to significant visual loss over a period of 9–10 months.^[13]

To overcome these lacunae in literature, we evaluated the real-world treatment outcomes of Razumab in n-AMD. We report the short-term visual outcomes, safety profile and the morphometric response on OCT biomarkers of disease activity in n-AMD.

Methods

It was a retrospective, interventional study of 20 eyes of 20 consecutive patients of active untreated n-AMD (Type 1 or Type 2 choroidal neovascular membrane [CNVM]) with PED who presented to the vitreoretinal services of a tertiary eye care center between October 2018 to January 2020. Patients with type 3 CNVM, or CNVM due to any other pathologies such as myopia, inflammatory, polypoidal choroidal vasculopathy (PCV) or pachychoroid neovasculopathy (PNV), or the simultaneous presence of other retinal pathologies such as diabetic retinopathy were excluded from the study. The study was conducted in accordance to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board. Written informed consent was obtained from each patient.

At baseline and each visit, all patients underwent detailed clinical evaluation, including assessment of best-corrected visual acuity (BCVA) on Snellen chart, intraocular pressure measurement (IOP) by Goldmann applanation tonometry, along with anterior segment and fundus evaluation by slit-lamp biomicroscopy and indirect ophthalmoscopy. Additionally, multimodal imaging was performed including swept-source optical coherence tomography (SS-OCT) (TOPCON, DRI Triton, JAPAN) and fundus fluorescein angiography (FFA) (TOPCON, DRI Triton, JAPAN) at baseline while SS-OCT was repeated at all visits.

Each eye received intravitreal injections of Razumab at the recommended dose of 10 mg/mL (0.05 mL) every 4 weeks for the first 3 months. The injections were given at baseline (week 0), at 4 weeks and at 8 weeks, respectively. After performing baseline evaluation along with first dose of injection at week 0, the patients were reviewed again at the end of 4 weeks, 8 weeks, and 12 weeks, respectively. All intravitreal injections were performed in an OT complex under strict aseptic precautions.

Image analysis

All imaging analysis was performed by a single masked observer (ASK). Automated central subfield thickness (CSFT) was calculated using the 25-line raster scan protocol.

A dense scan was carefully analyzed to look for maximum extent of PED and subsequently, their dimensions including the height and width were calculated using the built-in calipers [Fig. 1]. The PED was evaluated for type of reflectivity (hyper, hypo, mixed). Based on this they were classified as either serous PED (with clear optically empty sub-RPE space), drusenoid (sub-RPE space is filled with moderately reflective material), fibrovascular (where the sub-RPE space is filled with hyperreflective heterogeneous material), and hemorrhagic (where the surface appears highly reflective with shadowing due to the blood and the deeper layers are not seen) and mixed. The sections were also evaluated

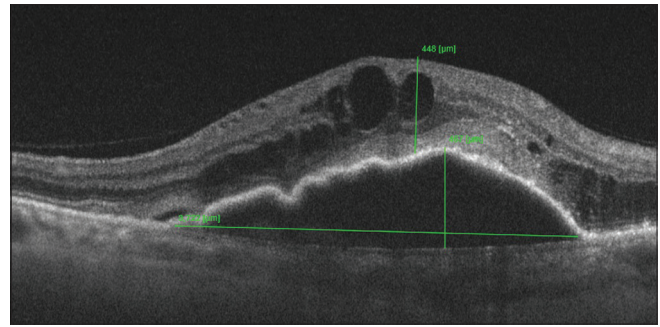


Figure 1: Swept-source optical coherence tomography (SS-OCT) image demonstrating measurements (Green lines) of the pigment epithelial detachment (PED) height, base diameter, and maximum retinal thickness (MRT)

for the presence or absence of intraretinal fluid (IRF) and subretinal fluid (SRF) and extent of maximum central retinal thickness (CRT) was manually measured.

Changes in BCVA, IRF, SRF, CSFT, CRT, and dimensions of PED were compared between baseline and all follow-up visits. Additional visual acuity outcomes included proportion of patients gaining or losing one line, two line, and three lines of Snellen VA from baseline at the end of 4 weeks, 8 weeks, and 12 weeks, respectively. Any ocular or systemic adverse events were also recorded.

The Statistical analysis was performed by SPSS 23.0 version (SPSS Inc., Chicago, Ill., USA). Continuous variables were described as mean and variation of each observation from the mean value (Standard deviation) represented as mean \pm standard deviation (SD), or median (Interquartile range; IQR) if they failed to follow a normal distribution. Paired data in comparison with baseline were analyzed with paired *t* test (normal distribution) or Wilcoxon signed-rank test (for nonnormal distribution). Categorical variables were described by taking percentages, paired data in comparison with baseline was analyzed using McNemar test. Variables with $P < 0.05$ was considered as statistically significant.

Results

Baseline characteristics [Table 1]

Twenty eyes of 20 patients with treatment naïve n-AMD and presence of PED were included in the study. The mean age of the study population was 68.85 ± 13.78 years, of which there were 10 eyes each of male and females, respectively. The median BCVA (logMAR) of the diseased eye was 1.38 (IQR 0.63 to 2 logMAR) while of the contralateral eye was 0.4 (IQR 0.2 to 1 logMAR). Fundus evaluation of the contralateral eye showed that eight eyes were normal, six eyes had dry AMD, two eyes had active n-AMD, 3 eyes had scarred n-AMD and one eye had geographic atrophy (GA), respectively.

On SS-OCT, PED was present in all 20 eyes with hyperreflectivity seen more frequently (17 eyes; 85%) than mixed reflectivity (3 eyes; 15%). All PED's were fibrovascular in nature. The median PED height was $264.5 \mu\text{m}$ (IQR $173.75 \mu\text{m}$ to $559.25 \mu\text{m}$), median PED width was $2017.5 \mu\text{m}$ (IQR $1024.5 \mu\text{m}$ to $3379 \mu\text{m}$), mean CMT was $338.75 \pm 101.5 \mu\text{m}$ and mean CRT was $373.75 \pm 90.58 \mu\text{m}$, respectively. SRF was noted in 12 eyes (60%) while IRF was seen in 6 eyes (30%), respectively.

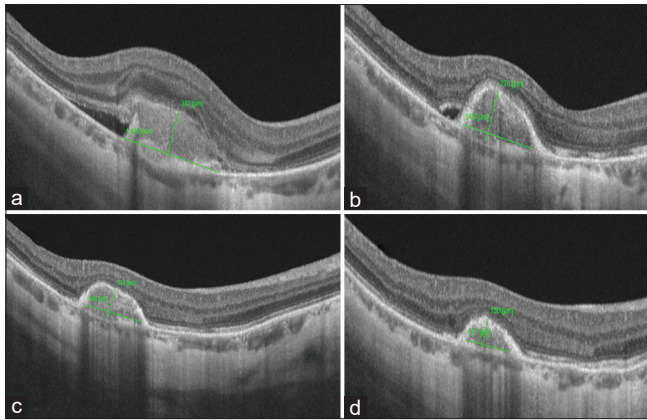


Figure 2: Serial Swept-source optical coherence tomography (SS-OCT) images of a patient with neovascular age-related macular degeneration (n-AMD) showing a gradual reduction in PED dimensions and resolution of subretinal fluid (SRF) after treatment with intravitreal ranibizumab biosimilar (Razumab) at weeks 4 (b), 8 (c) and 12 (d), respectively, from the baseline (a)

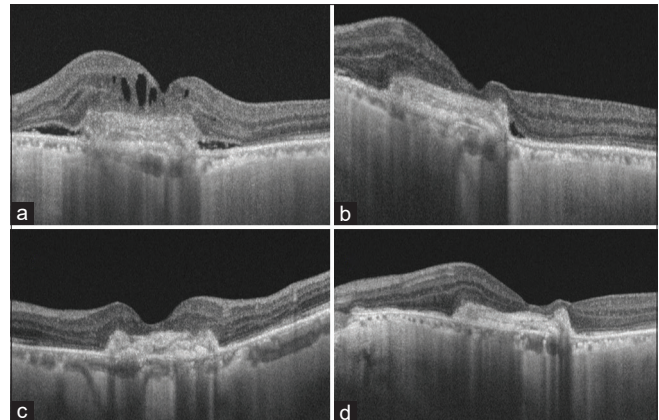


Figure 3: Serial Swept-source optical coherence tomography (SS-OCT) images of a patient with neovascular age-related macular degeneration (n-AMD) showing resolution of subretinal fluid and intraretinal fluid (IRF) after treatment with intravitreal ranibizumab biosimilar (Razumab) at weeks 4 (b), 8 (c) and 12 (d), respectively, from the baseline (a)

Table 1: Baseline characteristics of study eyes

Number of eyes		20
Age	Mean±SD	68.85±13.78
Gender		
Males	Number	10 (50)
Females	(Percentage)	10 (50)
Eye		
OD		9 (45)
OS		11 (55)
BCVA	Median (IQR)	1.38 (0.63-2)
Other eye BCVA	(logMAR)	0.4 (0.2-1)
Other Eye Status		
Phakic	Number	10 (50)
Pseudophakia	(Percentage)	10 (50)
PED reflectivity		
Hyper reflective		17 (85)
Mixed		3 (15)

SD: Standard deviation; BCVA: Best corrected visual acuity; IQR: Interquartile range; PED: Pigment Epithelial Detachment

Visual acuity changes [Table 2]

Compared to baseline, improvement in median BCVA (logMAR) was noted after each of the three loading doses of intravitreal Razumab (4 weeks -Median BCVA [logMAR]: 1.13 [IQR 0.7 to 1.83 logMAR], $P = 0.18$; 8 weeks - Median BCVA [logMAR]: 1.3 [IQR 0.6 to 2 logMAR], $P = 0.4$; 12 weeks - Median BCVA [logMAR]: 0.58 [IQR 0.43 to 1 logMAR], $P = 0.06$), although not statistically significantly. At weeks 4 and 8, six eyes each had ≥ 3 -line VA improvement which increased to eight eyes at 12 weeks. Nine eyes were stable at 12 weeks while one eye each had improvement of one-line, loss of one-line and loss of ≥ 3 -lines, respectively, at 12 weeks.

Morphometric changes in PED [Table 2]

None of the eyes showed complete resolution of PED. At weeks 4 and 8, there was an improvement in PED dimensions, although it was not significant. At 12 weeks, the PED height

reduced significantly from baseline (244 μm [IQR 176.25 μm to 386.5 μm], $P = 0.03$) while the reduction in PED width (1460 μm [IQR 817.5 μm – 2514 μm]; $P = 0.14$) was not significant [Fig. 2]. No change in reflectivity of PED or nature of PED (Fibrovascular/ Drusenoid/Serous/Hemorrhagic) was noted at any follow-up visits.

Other OCT biomarkers [Table 2]

At 4 weeks, no significant improvement was noted in CSFT (297.5 \pm 94.79 μm , $P = 0.12$) and CRT (338.4 \pm 82.13 μm , $P = 0.17$). However, by the end of 8 weeks and 12 weeks, statistically significant improvement was observed, both in CSFT (8 weeks: 238.3 \pm 105.59 μm , $P = 0.005$; 12 weeks: 240.25 \pm 51.01 μm , $P < 0.001$) and CRT (8 weeks: 297.65 \pm 69.83 μm , $P = 0.006$; 12 weeks: 294.25 \pm 58.54 μm , $P = 0.004$), respectively. Out of the six eyes with IRF at baseline, resolution was seen in four eyes at 4 weeks ($P = 0.13$) and 8 weeks (0.22), respectively, while it improved to five eyes at 12 weeks ($P = 0.13$). Among the 12 eyes with baseline SRF, complete resolution was seen in three eyes, five eyes and nine eyes at 4 weeks ($P = 0.38$), 8 weeks ($P = 0.04$) and 12 weeks ($P = 0.004$), respectively. The SRF resolution was statistically significant at end of 8 weeks and 12 weeks, respectively [Fig. 3].

Safety profile

Sixty injections were performed in this study. No ocular or systemic adverse events were observed during the study period.

Discussion

In the past decade, anti-VEGF agents have become the standard of care for various chorioretinal disorders such as n-AMD. Conversely, the treatment usually entails repeated courses of intravitreal injections over many years, thereby incurring high cumulative drug costs. This has prompted researchers to search for cost-effective alternatives such as biosimilars. Biosimilars are produced with reverse engineering techniques in living cell lines.^[14] Their safety, efficacy, structure, pharmacodynamics, and pharmacokinetic features closely resemble the approved biologics.^[14]

Table 2: Changes in visual acuity and swept source optical coherence tomography (SS-OCT) parameters from baseline through weeks 4, 8 and 12, respectively

Variables	Baseline	First Injection (Week 4)	P	Second Injection (Week 8)	P	Third Injection (Week 12)	P
BCVA	1.38 (0.63-2)	1.13 (0.7-1.83)	0.18	1.3 (0.6 to 2)	0.4	0.58 (0.43-1)	0.06
IRF	6 (30)	2 (10)	0.125	2 (10)	0.219	1 (5)	0.125
SRF	12 (60)	9 (45)	0.375	5 (25)	0.039	3 (15)	0.004
PED Height	Median (IQR) and 95% CI [Confidence Interval]	264.5 (173.75-559.25)[240-458]	0.1	229 (144.25-383) [201-323]	0.204	244 (176.25-386.5)[212-384]	0.033
PED Width	2017.5 (1024.5-3379)	1437.5 (986.25-2499)	0.204	1211.5 (912.25-2477.25)	0.445	1460 (817.5-2514)	0.135
CSFT	Mean±SD	338.75±101.5	0.118	238.3±105.59	0.005	240.25±51.01	<0.001
Maximal CRT	373.75±90.58	338.4±82.13	0.165	297.65±69.83	0.006	294.25±58.54	0.004

Best-corrected visual acuity (BCVA); IQR: Interquartile range; IRF: Intraretinal fluid; SRF: Subretinal fluid; PED: Pigment epithelial detachment; CSFT: Central-subfield thickness; CRT: central-retinal thickness; SD: Standard deviation

Razumab® is the first and only anti-VEGF biosimilar agent approved for intraocular use by Indian regulatory authorities.^[8] The RE-ENACT 2 trial evaluated the role of Razumab in wet AMD over 48 weeks.^[10] They demonstrated significant improvement in visual acuity from week 4 through week 48. Likewise, we also report similar improvement in vision at weeks 4, 8, and 12, respectively, although it was not significant. The majority of eyes in this study maintained stable visual acuity at end of 12 weeks (45%). Additionally, at 12 weeks, 40% of eyes had ≥ 3 -line VA improvement while only 5% of eyes lost ≥ 3 -line VA. On the whole, in our real-world experience with Razumab in n-AMD, we observed that 90% of patients either maintained (no change from baseline visual acuity at 12 weeks) or had improved visual acuity at 12 weeks' follow-up.

Retinal PEDs are typically encountered in patient with n-AMD. However, very limited studies have evaluated its response to ranibizumab and aflibercept therapy, while none has assessed the role of Razumab on PED morphometry. Improvement in PED height and volume has been demonstrated after intravitreal aflibercept treatment by Chan *et al.* at the end of 6 months.^[15] PanosGD have shown improvement in PED height after ranibizumab therapy at the end of 1 year.^[16] However, in literature, anatomical improvement in PED has not been correlated with functional improvement in visual acuity outcomes.^[17] In HARBOR study, the patients were treated until complete resolution of PED.^[18] Despite this, the PED reduction was not associated with better visual outcomes. Analogously, we also observed significant reduction in PED height at 12 weeks, but there was no statistically significant improvement in visual acuity. The HARBOR study has also shown that collapse of PED with aggressive anti-VEGF therapy led to worsening of vision with macular atrophy.^[17] Thus treating of PED till complete resolution may actually be detrimental to all patients.^[19]

Patients in this study experienced a definitive trend towards an improvement amongst all OCT biomarkers at the end of 12 weeks. Statistically significant improvement in CSFT and CRT was noted as early as 8 weeks and continued till 12 weeks. At week 12, the mean reduction in CSFT was 57.26 μm and CRT was 44.15 μm . The reduction in CSFT at 12 weeks is much lower as compared to the RE-ENACT 2 trial, where it was 143.41 μm .^[10] The MINERVA study which evaluated role of ranibizumab in wet AMD also showed superior anatomical outcome with a reduction in CSFT of 102.7 μm at 12 months.^[20] The earliest studies on short term outcomes of bevacizumab in n-AMD had shown a significant reduction in CSFT of around 85 μm while few other studies with aflibercept have documented no significant reduction, with a decrease in CSFT as low as 18 μm .^[21,22] Not many studies have evaluated change in CRT post anti-VEGF therapy, and none post Razumab. Wykoff *et al.* have shown a mean reduction in CRT of -246 μm for the monthly ranibizumab cohort and -173 μm for the treat-and-extend (TRES) cohort.^[23] In contrast, the CRT reduction in our study was comparably lower at 44.15 μm . Presence of IRF and SRF are considered important OCT biomarkers for disease activity in n-AMD. In the RE-ENACT 2 trial, the proportion of patients with IRF improved from 63.6% at baseline to 33.8% at 12 weeks and 15% at 48 weeks.^[10] Although in our study, IRF was seen only in 30% of eyes at baseline, it improved to 5% of eyes at week 12, a reduction of

25%. This reduction is similar to 29.8% seen at 12 weeks in the RE-ENACT 2 trial.^[10] Similarly, we noted resolution of SRF in 45% of eyes, which is slightly lower than 53.5% seen in the RE-ENACT 2 trial.^[10] The better response of OCT biomarkers to anti-VEGF therapy in literature could probably be explained by the differences in patient population, controlled environment and delivery settings of these traditional randomized controlled trials (RCTs), longer follow-up period, differences in the anti-VEGF molecules and sub-optimal therapeutic responses commonly reported in real-world settings.

One major unresolved issue with anti-VEGF therapy includes systemic safety. Ocular use of these agents has been associated with small increase in risk of systemic thromboembolic events, which may be significant in a few cases.^[24] Moreover, intraocular injections of biosimilars are capable of inciting immunologic reactions. Episodes of sterile endophthalmitis were reported after injections of Razumab in 2015, 2017 and 2019.^[25] Studies have shown the rate of infectious endophthalmitis to be around 0.035% after intravitreal injection of both ranibizumab and aflibercept.^[26] However, in our study, we did not encounter any case of ocular or systemic adverse events post Razumab injection.

Bevacizumab is a cost effective anti-VEGF for management of chorioretinal disorders. However, its use is limited due to issues with lack of FDA approval and compounding related complications such as endophthalmitis. Hence these is a gaping demand for a low-cost anti-VEGF which is efficacious and with a good safety profile, especially in developing world. Approved biosimilars such as Razumab which is economical and is available in a single-use vial, has the ability to fill this void. In this study, we performed a comprehensive evaluation of OCT biomarkers of disease activity in n-AMD. These micromorphic changes are very critical in visual prognosis. Although we did not note any significant improvement in BCVA, the results are too short term to assess the visual outcomes effects secondary to improvement in these OCT biomarkers. Nonetheless, the beneficial effect of Razumab on retinal morphometry can be postulated to have favorable long-term outcomes.

The limitations of our this study include its retrospective design, limited sample size, lack of control arm and short-term follow-up. Also, we did not perform an indocyanine green angiography (ICGA) in our study. Although ICGA remains the gold standard for diagnosing of PCV, there is growing consensus for noninvasive diagnoses of PCV. Multiple publications have demonstrated OCT-based criteria for diagnosing PCV and differentiating it from AMD.^[27-31] Very recently, a Consensus committee from the “Asia-Pacific Ocular Imaging Society PCV Workgroup” have published set of practical diagnostic criteria for PCV based on SD-OCT with high accuracy in clinical settings in which ICGA is not performed routinely.^[32] Although we did not perform ICG for our patients, the eyes with PCV/PNV were excluded from our study, based on other multimodal imaging features. One important strength of our paper is that the results reported here represent the first real-world data regarding the safety and efficacy of an emerging cost-effective anti-VEGF biosimilar with regulatory approval, namely Razumab, in n-AMD. Moreover, it is a singular real-world study to perform a detailed qualitative and quantitative assessment of Razumab on various morphological features on multimodal imaging, whereby we illustrate promising anatomical outcomes. The favorable

short-term visual, morphometric, and safety outcomes are indicative of similar potentially encouraging outcomes with long-term studies and larger sample size. Thereby we propose long-term follow-up studies with larger sample size to evaluate the detailed effects of Razumab in n-AMD.

Conclusion

In conclusion, our study demonstrates that use of intravitreal Razumab, an emerging and regulatory approved biosimilar to Lucentis, has promising morphological outcomes on SD-OCT, besides maintaining stable visual acuity with an acceptable safety profile. In addition, its low-cost favors its use as an efficacious anti-VEGF agent on a global scale as it can reduce the overall treatment cost by 25% to 50% as compared to branded drugs.^[14]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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